

A Stereoselective Palladium-Mediated Reductive Coupling of Electron-Deficient Terminal Iodoalkenes

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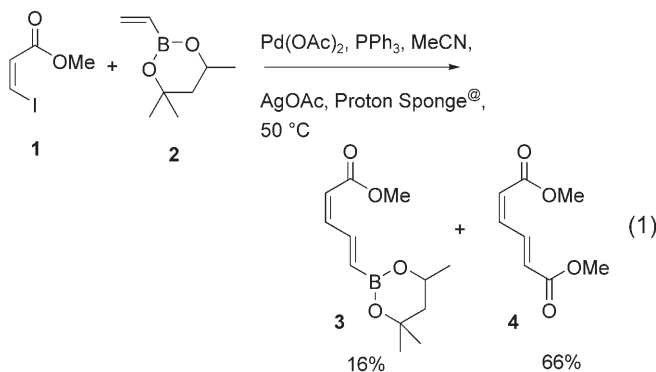


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Abstract: Iodoacrylate esters undergo palladium-catalysed reductive homocoupling to derive dienyldiester derivatives. This reductive coupling can be extended to ester-substituted terminal iododienes to derive tetraene diesters. In all cases, the reactions show relatively high levels of stereocontrol, which shows an inversion of stereochemistry about one iodoalkene unit. This process, and the suggestion that the reaction releases diiodine, is consistent with a *syn*-1,2-addition of an iodopalladium(II)-alkene species across another iodoalkene unit (carbometallation step), followed by reductive *syn*-elimination of iodopalladium iodide to derive palladium(II) iodide. It appears that under the reaction conditions employed, palladium(II) iodide may equilibrate to palladium(0) and diiodine, which can be observed or trapped out from the reaction mixture.

Keywords: alkenes; C–C coupling; electron-deficient compounds; palladium; reduction; stereoselectivity

is typically poor.^[8] As part of our endeavours^[9] to construct viridenomycin,^[10] palladium-catalysed cross-coupling reactions have been examined involving methyl *Z*-iodoacrylate **1** and a vinylboronate ester^[11] **2** which resulted in complications, rather than Heck–Mizoroki coupling of the vinylboronate.^[12] These chemoselectivity problems were circumvented by use of kinetic and optimisation studies^[13] such that methyl *Z*-iodoacrylate **1** could be selectively coupled to give solely the Heck–Mizoroki product **3**. However, a product resulting from stereoselective homocoupling of the acrylate was isolated [Eq. (1)] and a mecha-

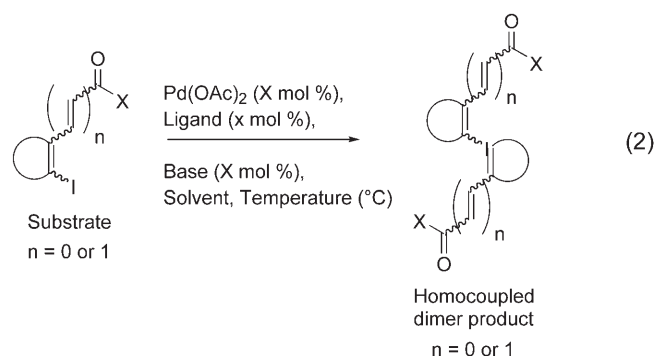


The reductive homocoupling of aryl and alkenyl halides is a synthetically useful reaction and has received much attention.^[1] Three general methods have been reported: i) transformation to the corresponding organolithium^[2] or Grignard^[3] and metal-catalysed homocoupling; ii) the copper-promoted Ullmann coupling;^[4] and iii) the nickel-^[5,6] or palladium^[7]-promoted coupling. Each method has significant drawbacks; use of organolithium and Grignard reagents may be precluded by other functionality within the molecule, Ullmann couplings typically require high temperatures as well as stoichiometric copper and although the nickel- and palladium-promoted process can be made catalytic through the use of a stoichiometric reductant, the stereoselectivity seen for alkenyl halides

is typically poor.^[8] As part of our endeavours^[9] to construct viridenomycin,^[10] palladium-catalysed cross-coupling reactions have been examined involving methyl *Z*-iodoacrylate **1** and a vinylboronate ester^[11] **2** which resulted in complications, rather than Heck–Mizoroki coupling of the vinylboronate.^[12] These chemoselectivity problems were circumvented by use of kinetic and optimisation studies^[13] such that methyl *Z*-iodoacrylate **1** could be selectively coupled to give solely the Heck–Mizoroki product **3**. However, a product resulting from stereoselective homocoupling of the acrylate was isolated [Eq. (1)] and a mechanism proposed involving palladium-enolate species resulting in a reductive dimerisation product **4** of the iodoacrylate.^[13] We now report that this type of reductive dimerisation is a general phenomenon for electron-deficient terminal iodoalkenes and polyenes, and that such processes are unlikely to proceed through palladium-enolate species.

The discovery of homocoupled product **4** (as a 25:5:1 mixture of *E,Z:E,E,Z,E*-stereoisomers) from Eq. (1)^[12] prompted a closer examination of palladium-mediated cross-coupling reactions involving terminal iodoalkenes under a variety of reaction conditions.

After considerable experimentation, it was found that the formation of the reductive dimer **4** is palladium-mediated, does not require either a phosphine ligand or vinylboronate to be present, and seems to be most efficient when using Proton Sponge® and silver(I) salts, though it occurs more or less efficiently under a variety of conditions, as outlined in Eq. (2) with the



corresponding results in Table 1, and appears to be a process which is characteristic of terminal, unsubstituted, ester-conjugated iodoalkenes.

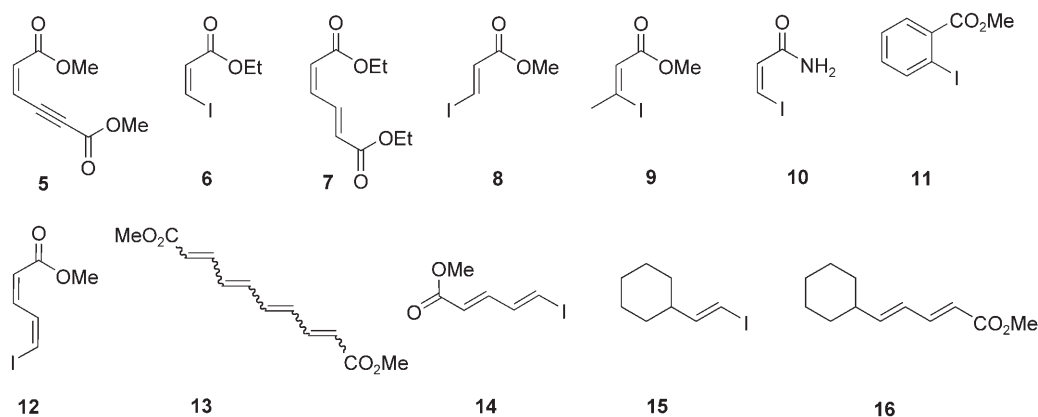
cis-Iodoacrylate **1** was examined under a range of reaction conditions (entries 1–5, Table 1), which demonstrated that running the reaction with a 5 mol % palladium loading, a small excess of both Proton Sponge® and silver(I) acetate, in acetonitrile at 50 °C results in a 44 % yield of dimer **4** after silica gel chromatography (entry 1). Increasing the catalyst, Proton Sponge® and silver(I) loading improves the isolated yield, however, at the expense of a minor loss of stereocontrol (entry 2) from a 24:1 to a 17:1 mixture of the *E,Z*- and *E,E*-diastereoisomers respectively. Using a more polar solvent than in entry 1 (DMF, entry 3) at the same temperature (50 °C) results in considerably reduced dimer **4** yield, however, with an almost doubling in the stereocontrol in favour of the *E,Z*-isomer (55:1, *E,Z:E,E*). Entry 4 (Table 1) demonstrates that Proton Sponge® and a silver(I) salt are not absolutely necessary, since dimer **4** is produced, albeit in only 30 % yield and relatively poor stereocontrol (12:1, *E,Z:E,E*), together diiodine (as indicated by a purple colouration of the reaction mixture).

Changing the palladium source from palladium(II) acetate (entry 1, Table 1) to the iodide (entry 5) shows that palladium(II) iodide is an active catalyst, though it appears to be less efficient than the catalytic species generated from palladium(II) acetate in terms of yield. However, the stereocontrol is improved from 24:1, *E,Z:E,E* to 50:1. In addition, a small amount of the Sonogashira product **5**^[13] is also formed, presumably by coupling of methyl propiolate, generated *in situ* from elimination of HI from acrylate **1**.

Changing the carboxylate iodoalkene substitution has interesting effects. Simple ester derivatisation of methyl (entry 1, Table 1) to ethyl ester (entry 6) has a small effect in terms of yield (44 to 53 %) and stereocontrol (24:1 to 33:1). Changing the iodoalkene geometry from *cis* to *trans* (entry 7, Table 1) has quite a dramatic effect compared with entry 2; yield drops from 57 to 22 %, and the stereocontrol drops from 17:1 to only 4:1 (*E,Z:E,E*). In addition, increasing substitution on the iodoalkene (entry 8), replacing the acrylate ester with an amide function (entry 9) and using an *ortho*-iodobenzoate ester (entry 10) all result in no observable reaction. In contrast, increasing the length of the iodoalkene to a dienyl iodide, whether *Z,Z*-iodopentadienoate **12** (entry 11, Table 1), or the corresponding *E,E*-isomer **14** (entry 12) has a beneficial effect resulting in a 90 and 64 % yield of the corresponding homocoupled dimer **13**. However, the stereochemical outcomes are very different; the all-*cis*-iododiene **12** results in a mixture of three of the possible stereoisomers, with the *Z,E,E,E*- and *E,Z,E,E*-isomers being the major products, whereas the all-*trans*-iododiene **14** provides essentially a single stereoisomer (*E,Z,E,E*) with only a trace of the *Z,E,E,E*-isomer detectable by high-field NMR.

Most odd of all the reactions carried out to date, was the reaction outlined by entry 13 (Table 1), in which the reaction conditions from entry 4 were reproduced, with the addition of starch to the reaction mixture to assist with the removal of diiodine which is produced in this reaction (*vide supra*). The addition of starch does indeed improve the conversion of *cis*-iodoalkene **1** to dimer **4** (30 to 50 %), however, there are major changes in the stereochemical outcome, from a 12:1 mixture of *E,Z* and *E,E* isomers, respectively, to a surprising 1:2:3.7 mixture of *E,Z:E,E:Z,Z*, i.e., with the all-*cis*-diene being the major isomer and the only conditions under which this isomer has been observed. Little is known about the affinity and loading capability of starch for diiodine, especially in an aqueous phase, although gas phase measurements have been carried out to give predictions of 10–30 % being possible.^[15] For this application, a loading of approximately 18 % would in theory be required, however, we cannot be certain at this stage about the mechanism of the diiodine absorption, nor whether palladium is also absorbed onto the starch to account for the different stereochemical outcome to the non-starch-based reactions.

The final entry in Table 1, e.g., **14**, is a reaction which involves the electron-deficient *cis*-iodoacrylate **1** and the relatively electron-rich *trans*-iodoalkene **15**. To our surprise, the dienyl diester **4** was not the sole product, though it was the major product (77 %) and showed the expected high level of stereocontrol for inversion of stereochemistry at one iodoalkene unit. A more minor product, 18 % with respect to **1**, was

Table 1. Reductive coupling reactions involving different alkenyl iodides.

Entry	Substrate/s	Product/s (Yield [%]) ^[a]	Stereoselectivity	Conditions (equivalents)
1	1	4 (44)	<i>E,Z:E,E:Z,Z</i> = 24:1:0	Pd(OAc) ₂ , (0.05), Proton Sponge [®] (1.2), AgOAc (1.05), MeCN, 50 °C
2	1	4 (57)	<i>E,Z:E,E:Z,Z</i> = 17:1:0	Pd(OAc) ₂ , (0.10), Proton Sponge [®] (2.4), AgOAc (2.4), MeCN, 50 °C
3	1	4 (23)	<i>E,Z:E,E:Z,E</i> = 55:1:0	Pd(OAc) ₂ , (0.05), Proton Sponge [®] (1.6), AgOAc (1.5), DMF, 50 °C
4	1	4 (30)	<i>E,Z:E,E:Z,Z</i> = 12:1:0	Pd(OAc) ₂ , (0.05), PPh ₃ (1.5), Na ₂ CO ₃ (3.5), THF:H ₂ O (9:1), 70 °C
5	1	4 (21) + 5 (4)	<i>E,Z:E,E:Z,Z</i> = 50:1:0	PdI ₂ , (0.05), Proton Sponge [®] (1.5), AgOAc (1.4), MeCN, 50 °C
6	6	7 (53)	<i>E,Z:E,E:Z,Z</i> = 33:1:0	Pd(OAc) ₂ , (0.07), Proton Sponge [®] (1.5), AgOAc (1.3), MeCN, 50 °C
7	8	4 (22)	<i>E,Z:E,E:Z,Z</i> = 4:1:0	Pd(OAc) ₂ , (0.10), Proton Sponge [®] (2.4), AgOAc (2.4), MeCN, 50 °C
8	9	No reaction	n/a	Pd(OAc) ₂ , (0.07), Proton Sponge [®] (1.6), AgOAc (1.5), MeCN, 50 °C
9	10	No reaction	n/a	Pd(OAc) ₂ , (0.07), Proton Sponge [®] (1.6), AgOAc (1.5), MeCN, 50 °C
10	11	No reaction	n/a	Pd(OAc) ₂ , (0.05), Proton Sponge [®] (1.6), AgOAc (1.5), MeCN, 50 °C
11	12	13 (90)	<i>Z,E,E,Z:Z,E,E,E:Z,E,E</i> = 1:4.3:4.6	Pd(OAc) ₂ , (0.05), Proton Sponge [®] (1.6), AgOAc (1.5), MeCN, 50 °C
12	14	13 (64)	<i>E,Z,E,E:Z,E,E,E</i> = > 20:1	Pd(OAc) ₂ , (0.05), Proton Sponge [®] (1.6), AgOAc (1.5), MeCN, 50 °C
13	1	4 (50)	<i>E,Z:E,E:Z,Z</i> = 1:2:3.7	Pd(OAc) ₂ , (0.05), PPh ₃ (0.11), Na ₂ CO ₃ (3.4), Starch (700 g mol ⁻¹), THF:H ₂ O (9:1), 70 °C
14	1 + 15	4 (77 ^b) + 16 (18 ^[b]) (25 ^[c]) + recovered 15 (61)	4 : <i>E,Z:E,E:Z,Z</i> = 20:1:1; 16 : <i>E,Z:E,E</i> = > 20:1	Pd(OAc) ₂ , (0.05), Proton Sponge [®] (1.6), AgOAc (1.5), MeCN, 50 °C

^[a] All reactions conducted over 20 h.

^[b] Yield based on **1** consumed.

^[c] Yield based on **15** consumed.

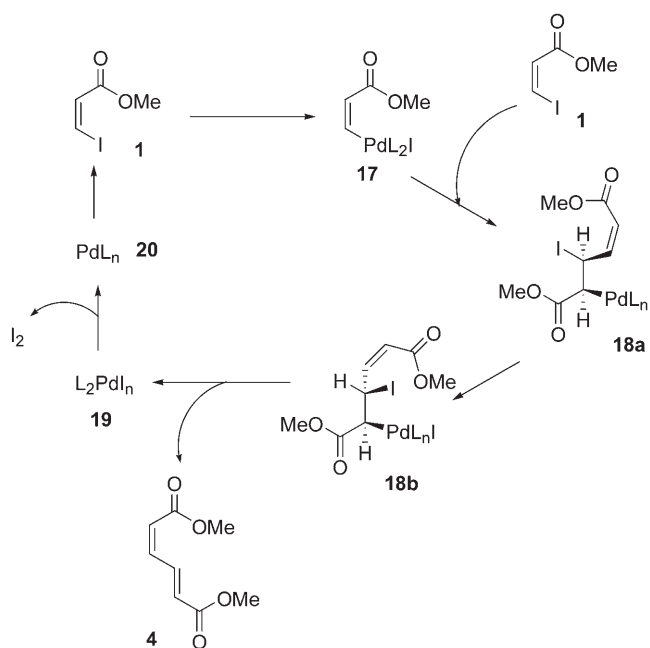
the heterodimer product **16**, notably showing the same major inversion across the acrylate iodoalkene bond. This suggests that the dimerisation process may be more dependent upon having an electron-deficient iodoalkene as an electrophilic acceptor, rather than necessarily requiring an intermediate palladium(II)-

iodoalkene complex with an electron-withdrawing group. The fact that the major product derives from acrylate **1** dimerisation is likely to be a reflection of the relative rates of the formation of the iodopalladium(II)-alkene complex from an electron-deficient iodoalkene *versus* and electron-rich iodoalkene. It is

also noteworthy that this reaction (entry 14) produces the highest yield of reductive dimerisation, however, unreacted iodoalkene is recovered in high yield accounting for 86% of the starting iodoalkene **15**, hence **15** is not responsible for reacting with the diiodine by-product although its facilitation of the overall dimerisation process is clearly inferred.

The results (Table 1) necessarily require a revision of our previously proposed mechanism.^[13] The finding of the formation of reductive dimer **4** from the reaction described in Eq. (1) led us propose a palladium(II) acrylate-iodide complex undergoing Michael-type addition to provide a palladium(II)-enolate species. However, there is a clear indication of predominant inversion of iodoalkene stereochemistry upon reductive dimerisation even with iodiene systems. This is exemplified by entries 1–7 which all demonstrate that the major isomer results from geometry inversion across one coupling partner, and dienyliodide **14** results in highly selective formation of the *E,E,Z,E*-isomer (entry 12) which requires selective olefin inversion across one terminal alkene. With the *Z,Z*-dienyliodide **12**, the expected major product stereoisomer would have the *Z,Z,E,Z*-tetraene geometry, however, this is not observed, even in the crude reaction mixture. However, in this case of tetraenes **13**, there are clear indications of thermodynamic instability and the isolated ratio of stereoisomers is unlikely to reflect the kinetic product ratio directly as a result of the reductive coupling. For example, CDCl_3 solutions of either *Z,E,E,Z*- or *Z,E,E,E*-tetraene **13** undergo slow isomerisation in ambient light over a few months, eventually providing the all-*trans*-(*E,E,E,E*)-isomer. Similar effects result from heating toluene solutions at 110 °C over a matter of hours, with the *Z,E,E,E*-isomer being slowest to isomerise. Taken together, we propose the broad overall mechanistic process outlined in Scheme 1 to explain the generally major product formation, i.e., involving a palladium(II) complex **17** from addition of a palladium(0) complex to iodoalkene **1**, *syn*-addition another iodoalkene **1** to provide C-attached^[14] intermediate **18a**. Bond rotation to allow *syn*-elimination can occur from conformation **18b**, resulting in reductive dimer **4** and the palladium(II) iodide complex **19**, from which diiodine is lost to return palladium(0) complex **20**.

The fate of the resulting diiodine is still in question, however, as previously noted, certain reactions (such as entry 4, Table 1) appear to have free diiodine present, suggesting that the palladium(II) iodide complex **19** undergoes facile reductive elimination of diiodine. In addition, none of the reactions examined to date provide quantitative reductive dimerisation product formation, hence, it is very likely that diiodine can react with both the starting materials, such as **1** (known reaction for iodoacrylate isomerisation^[13]), or the products, resulting in non-isolable products. For



Scheme 1. Proposed mechanistic scheme for the reductive dimerisation of terminal, electron-deficient iodoalkenes exemplified by *Z*-iodoacrylate **1**.

the more efficient reactions involving silver(I) and Proton Sponge®, it is also possible that silver(I) acts as a reducing agent for diiodine, however, we believe that Proton Sponge® is more important for removing diiodine from the reaction. Evidence of this is preliminary, however, heating a 1:1 mixture of palladium(II) iodide and Proton Sponge® dissolved in MeCN-d_3 at 50 °C slowly produces an unsymmetric Proton Sponge® adduct in which the aromatic system is intact. This process is considerably faster in the presence of silver(I) acetate, and if the reaction is carried out at 70 °C for 24 h eventually results in reaction on the aromatic ring, presumably resulting in ring iodination, though the products are unstable and to date have not been isolated or characterised. Considerable further work is required to obtain a detailed understanding of the unusual processes operating in these types of reductive dimerisation reactions, however, even at this stage, the dimerisation of terminal iodoalkenes can be useful for the highly stereoselective synthesis of polyenes, particularly substituted by electron-withdrawing groups. This area of polyene synthesis is still rather underdeveloped and invariably produces the all-*trans*-isomers, which does not occur with reductive dimerisation except by thermodynamic equilibration (*vide supra*). For example, *E,E,E*-1,8-hexatrienoate derivatives have been prepared by photochemical,^[16] *E,E,E,E*-1,10-hexatetraenoic acid has been prepared by alkyne or tetraene isomerisation, as have the corresponding penta- and hexa-ene analogues,^[17] and by using Wittig-related methods.^[18] In

contrast, the reductive coupling approach allows the rapid construction of other isomers of such electron-deficient polyene systems, which may have benefit not only for polyene-containing natural product synthesis^[19] but also for application as molecular wires.^[20] In addition, the continued study of this type of process is likely to result in potentially efficient approaches to otherwise inaccessible polyene geometries. Entry 13 in Table 1 clearly shows the potential for future developments, in this case not only producing some of the all-*cis*-diene **4**, but these reaction conditions also avoid the use of expensive silver(I) salts and Proton Sponge.®

Although these results are clearly preliminary, they do show that there is still much to be learnt about palladium coupling reactions. In addition, this type of reductive homocoupling has the potential to be another useful tool for the rapid assembly of polyenyl systems, with moderate to high stereocontrol. The initial signs of heterodimerisation of different iodoalkenes have also been demonstrated, which potentially widens the scope of such reactions enormously, and clearly has mechanistic repercussions. Further investigations into these highly stereocontrolled, efficient reductive dimerisation reactions of terminal haloalkenes is underway, particularly with respect to the mechanism and fate of the diiodine by product.

Experimental Section

Synthesis Dienyl Diester **4** (Table 1, entry 2)

To a dried Schlenk tube under a positive pressure of argon was added **1** (267 mg, 1.25 mmol) and dry MeCN (7 mL), the mixture was degassed using the freeze-pump-thaw method (1×), palladium(II) acetate (27.5 mg, 0.12 mmol), Proton Sponge (650 mg, 3 mmol) and silver(I) acetate (500 mg, 3 mmol) were added, then the mixture was further degassed using the freeze-pump-thaw method (2×) and heated to 50 °C under argon. After 20 h the reaction mixture was cooled, diluted with Et₂O (70 mL), passed through Celite and washed with 5% HCl (30 mL) and brine (30 mL). Drying (MgSO₄) gave crude product as a brown solid. Purification by silica gel chromatography (EtOAc:petroleum ether, 1:4) gave **4**; yield: 61 mg (57%). All spectroscopic and analytical properties for *E,E*-,^[5] *Z,Z*-,^[5] and *E,Z*-isomers^[1] were identical to those reported.

(*2Z,4E*)-Diethyl Hexa-2,4-dienedioate **7**

To a dried Schlenk tube under a positive pressure of argon was added **6** (400 mg, 1.77 mmol) and dry MeCN (15 mL), the mixture was degassed using the freeze-pump-thaw method (1×), palladium(II) acetate (27 mg, 0.12 mmol), silver(I) acetate (387 mg, 2.3 mmol) and Proton Sponge (585 mg, 2.7 mmol) were added, then the mixture was further degassed (2×) and heated to 50 °C. After 20 h the mixture was cooled, diluted with Et₂O (100 mL), passed through Celite and washed with 5% HCl (35 mL) and brine

(35 mL). Drying (MgSO₄) and evaporation gave crude product as a brown oil. Purification by silica gel chromatography (EtOAc:petroleum ether, 1:9) gave **7** as a pale yellow oil, yield: 92 mg (53%).

Reductive Dimerisation of Iodide **12**

To a dried Schlenk tube under a positive pressure of argon was added palladium(II) acetate (7.5 mg, 0.033 mmol), silver(I) acetate (168 mg, 1.0 mmol), Proton Sponge (229 mg, 1.1 mmol) and a solution of iodide **12** (160 mg, 0.67 mmol) in dry MeCN (6 mL), the mixture was degassed using the freeze-pump-thaw method (3×) and heated to 50 °C with vigorous stirring. After 19.5 h the mixture was cooled, diluted with Et₂O (60 mL), passed through Celite and washed with 5% HCl (20 mL) and brine (20 mL). Drying (MgSO₄) and evaporation gave crude product as a brown solid. Purification by silica gel chromatography (EtOAc:pet. ether, 1:19 then 1:9) gave *Z,E,E,Z*-**13** (mp 110–112 °C, yield: 7 mg, 9%), *Z,E,E,E*-**13** (mp 98–100 °C, yield: 29 mg, 39%) and *E,Z,E,E*-**13** (yield: 31 mg, 42%), all pale yellow solids.

Synthesis of Iodide **14**

To a dried Schlenk tube under a positive pressure of argon was added a solution of the corresponding diene boronate methyl ester,^[1] (230 mg, 0.965 mmol) in dry THF (5.5 mL), and the tube cooled to –78 °C in the absence of light. NaOMe (2.4 mL of a 0.5 M solution in MeOH, 1.2 mmol) was added dropwise, the mixture stirred for 30 min and ICl (1.5 mL of a 1 M solution in DCM, 1.50 mmol) added dropwise. The mixture was stirred for 1 hour, warmed to room temperature, diluted with diethyl ether (65 mL) and washed with 5% aqueous sodium metabisulfite (35 mL), water (35 mL), and brine (35 mL). Drying (MgSO₄) and evaporation gave the crude product as a yellow solid which was purified by silica gel chromatography (EtOAc:petroleum ether, 5:95) to give **14** as a white powder; yield: 206 mg (90%), mp 56–61 °C (decomposition). Recrystallisation by cooling a hexane solution gave crystals suitable for X-ray diffraction.

Reductive Dimerisation of Iodide **14**

To a dried Schlenk tube under a positive pressure of argon was added iodide **14** (100 mg, 0.42 mmol), palladium(II) acetate (5 mg, 0.02 mmol), silver(I) acetate (105 mg, 0.63 mmol), Proton Sponge (143 mg, 0.67 mmol) and dry MeCN (4 mL), then the mixture was degassed using the freeze-pump-thaw method (3×) and heated to 50 °C with vigorous stirring. After 20 h the mixture was cooled, diluted with Et₂O (30 mL), passed through Celite and washed with 5% HCl (10 mL), water (10 mL) and brine (10 mL). Drying (MgSO₄) and evaporation gave the crude product as a yellow solid. Purification by silica gel chromatography (EtOAc:petroleum ether, 5:95 then 1:9) gave *E,Z,E,E*-**13** as a white solid; yield: 30 mg (64%).

2-[(*E*)-2-Cyclohexylvinyl]-4,4,6-trimethyl-1,3,2-dioxaborinane

Stirred cyclohexylacetylene (3 mL, 23 mmol) was cooled to 0 °C under argon, catecholborane (2.55 mL, 26 mmol) added

dropwise and the mixture heated to 70 °C. After 2 h the mixture was cooled to room temperature, diluted with water (5 mL) and stirred for 30 min before the addition of saturated aqueous NaHCO₃ (20 mL) and a solution of 2-methylpentane-2,4-diol (3.3 mL, 26 mmol) in Et₂O (10 mL). The solution was stirred vigorously for 100 min, diluted with Et₂O (50 mL) and water (25 mL), separated, washed with saturated aqueous NaHCO₃ (40 mL), water (40 mL) and brine (20 mL), dried (MgSO₄) and evaporated to give the crude product as a pale brown oil. Cooling to –15 °C caused precipitation and the mixture was extracted with Et₂O/petroleum ether (5:95, 3 × 5 mL) and the solution purified by silica gel chromatography (Et₂O:petroleum ether, 5:95) to give 2-[(*E*)-2-cyclohexylvinyl]-4,4,6-trimethyl-1,3,2-dioxaborinane as a pale yellow oil; yield: 4.33 g (89 %).

[(*E*)-2-Iodovinyl]cyclohexane 15

To a solution of 2-[(*E*)-2-cyclohexylvinyl]-4,4,6-trimethyl-1,3,2-dioxaborinane (274 mg, 1.30 mmol) in THF (7 mL) was added NaOMe (3.0 mL of a 0.5 M solution in MeOH, 1.5 mmol) dropwise, the mixture stirred for 15 min prior to the addition of ICl (1.5 mL of a 1.0 M solution in DCM, 1.5 mmol) and the mixture stirred at room temperature in the absence of light. After 1 h the mixture was diluted with Et₂O (60 mL), washed with 5 % aqueous sodium metabisulphite (20 mL), water (40 mL) and brine (20 mL), dried (MgSO₄) and evaporated to give the crude product as a yellow oil. Purification by silica gel chromatography (petroleum ether) gave **15** as a clear oil; yield: 174 mg (62 %).

(2*E*,4*E*)-Methyl 5-Cyclohexylpenta-2,4-dienoate 16

To a dried Schlenk tube under a positive pressure of argon was added palladium(II) acetate (18 mg, 0.08 mmol), silver(I) acetate (280 mg, 1.6 mmol), Proton Sponge (390 mg, 1.8 mmol), dry MeCN (10 mL), **15** (184 mg, 0.78 mmol) and **1** (236 mg, 1.1 mmol), then the mixture was degassed using the freeze-pump-thaw method (3 ×) and heated to 50 °C under argon. After 20 h the reaction mixture was cooled, diluted with Et₂O (80 mL), passed through Celite and washed with 5 % HCl (30 mL) and brine (30 mL). Drying (MgSO₄) gave crude product as a brown oil. Purification by silica gel chromatography (gradient elution, EtOAc:petroleum ether, 0:1 to 15:85) gave **15** (yield: 113 mg, 61 %), **16** (yield: 38 mg, 18 % based on **1**, 25 % based on **15**) and **4** (yield: 72 mg, 77 %).

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